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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/715,272	06/14/91	CARTER	F 709

EXAMINER
FEISEE, L

ART UNIT | PAPER NUMBER
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GENENTECH, INC.
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DATE MAILED: 02/03/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/17/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 12 and 13 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-11, 14-21 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 12 and 13 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The finality of the previous Office action is withdrawn in view of the following new grounds of rejection.

Claims 12 and 13 are pending in this application, and these claims are humanized light and heavy chain variable regions of a previously referenced antibody 4D5.

Claims 12 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Hudziak et. al. or Fendly et. al. in view of Queen et. al.

Hudziak et. al. and Fendly et. al. both teach the production and characterization of the 4D5 antibody (see Hudziak et. al. 1166-1167 and Fendly et. al. pages 1553-1554). Hudziak et. al. suggests the possible therapeutic role of the 4D5 antibody in human neoplasias which overexpress p185-HER2 (pages 1171, last paragraph) while Fendly et. al. disclose the possible use of anti-p185 HER2 antibodies for in vivo radioimaging for detection of relevant primary tumors. They do not describe the production of these antibodies in the humanized form.

Queen et. al. teach the production of antibodies against IL-2 receptor in the humanized form, using computer modeling in order to determine the modification of certain framework regions in conjunction with CDR grafting. The antibodies produced are than to be used for in vivo administration to human patients, either for diagnosis or therapy. It is known in the art that murine and even chimeric antibodies have characteristics which may severely limit their use in human therapy. As foreign proteins, murine and chimeric antibodies may elicit immune reactions that reduce or destroy their therapeutic efficacy and/or evoke allergic or hypersensitivity reactions in patients. The probable need for readministration of such therapeutic modalities in neoplastic

disorders increases these risks. The result would be tissue injury by virtue of antigen-antibody deposition.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make humanized antibodies having the sequences of the 4D5 antibody. The methods of Queen et. al. were clear and self explanatory, and resulted in a high affinity antibody. One of ordinary skill in the art would have been motivated to humanize the 4D5 antibody in light of its potential therapeutic and diagnostic applicability.

Although the claims are drawn to specific amino acid sequences, it is maintained that the differences in amino acid sequence which would have been obtained using the method of Queen et. al. would not have been patentably distinct from the claimed amino acid sequences. Absent sufficient factual evidence to the contrary the claims are obvious over the cited prior art.

35 U.S.C. § 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.**

Claims 12 and 13 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. These claims are drawn to a light chain variable region polypeptide and a heavy chain variable region polypeptide which in and of themselves have no patentable utility. The specification does not disclose any

practical utility for the individual polypeptides and does not present evidence that these polypeptides are capable of binding in any particular manner when not in association with each other.

Claims 12 and 13 are directed to an invention not patentably distinct from claims 1, 3-9, and 40 of commonly assigned 07/977,453.

Specifically, the claims of the instant invention are drawn to the humanized version of the 4D5 antibody which is disclosed in copending application.

Commonly assigned 07/977,453, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. 1.78(c) and 35 U.S.C. § 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

Claims 12 and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,3-9, and 40 of copending application Serial No. 07/977,453 in view of Queen et. al.. The instant claims are drawn to the heavy chain and light chain variable regions of the 4D5 antibody. Copending application 07/977,453 claims an antibody with the same characteristics as 4D5, and also states within the claims that 4D5 antibody was useful for diagnosis and therapy of tumors expressing the p185 HER2 antigen on their surface. The induction of HAMA responses upon repeated administration of rodent antibodies has led to the desirability of producing antibodies which are even more "near human" than chimeric antibodies. Queen et. al. describes the production of antibodies which contain essentially the CDR of rodents and are grafted into human framework regions. These antibodies are also mutated in certain framework residues in order to produce functional and high affinity molecules. The procedure in Queen et. al. clearly teaches the particular framework residues that need to be changed in order to yield high affinity antibodies, and they teach how to determine the appropriate residues using computer modeling programs. This protocol is adaptable to any number of antibodies. Therefore, not only was the production of non-immunogenic 4D5 antibodies desirable, but the procedure for producing the antibodies was also well known and practiced. It would have been prima facie obvious

to one of ordinary skill in the art at the time the invention was made to use the claims of the copending application in combination with the reference of Queen et. al. in order to obtain high affinity functional humanized antibodies.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 U.S.P.Q. 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.78(d).

Claims 12 and 13 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/977,453 in view of Queen et. al.

The instant claims are drawn to the heavy chain and light chain variable regions of the 4D5 antibody. Copending application 07/977,453 discloses an antibody with the same characteristics as 4D5, and also discloses that 4D5 antibody is useful for diagnosis and therapy of tumors expressing the p185 HER2 antigen on their surface. The induction of HAMA responses upon repeated administration of rodent antibodies has led to the desirability of

producing antibodies which are even more "near human" than chimeric antibodies. Queen et. al. describes the production of antibodies which contain essentially the CDR of rodents and are grafted into human framework regions. These antibodies are also mutated in certain framework residues in order to produce functional and high affinity molecules. The procedure in Queen et. al. clearly teaches the particular framework residues that need to be changed in order to yield high affinity antibodies, and they teach how to determine the appropriate residues using computer modeling programs. This protocol is adaptable to any number of antibodies. Therefore, not only was the production of non-immunogenic 4D5 antibodies desirable, but the procedure for producing the antibodies was also well known and practiced. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the claims of the copending application in combination with the reference of Queen et. al. in order to obtain high affinity functional humanized antibodies.

Copending application Serial No. 07/977,453 has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lila Feisee whose telephone number is (703) 308-2731.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Feisee/lf
January 11, 1994

PAULA K. HUTZELL
PRIMARY EXAMINER
GROUP 1800